REMARKS

Upon entry of this amendment claims 53 and 55 have been amended, claims 60-63 are added, claims 53, 55-57 and 60-63 are pending and claims 56 and 57 are withdrawn. Claim 53 has been amended to add the recitations of previously pending claim 58. New claims 60-63 are based on the subject matter of claims 55-57.

Claim Rejections – 35 USC § 102(e)

Claim 34 has been canceled rendering moot the previous rejection under 35 USC 102(e).

Claim Rejections – 35 USC § 103(a)

The subject matter of previously pending claim 58, now incorporated into claim 53, has been rejected under 35 USC 103(a) as being obvious over US Patent No. 6,552,060 (Kirkpatrick) and Konings *et al.*, *J. Med. Chem.* 1996, 39, 2710-2719 (Konings) and US Patent No. 4,766,133 (Fischli). Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

I. Combination of Kirkpatrick and Konings

The outstanding rejection for obviousness depends in part on the combination of Kirkpatrick, who teaches assaying disulfides library members separately in a microtiter plate, with Konings, whose paper relates to RNA hybridization as a theoretical model of library deconvolution. The Examiner has stated that the theoretical RNA hybridization model of Konings "could be used interchangeably" with the teachings of Kirkpatrick as "both methods were well known in the art at the time of filing." (Advisory Action dated 11/17/2004, page 6, last paragraph.) The Examiner has also maintained that the teachings of Konings could be applied to "all compounds" and that "[c]ombinatorial chemistry has been virtually applied to every area of chemistry without limit." (Id., page 8, last paragraph.) In support of the universality of the Konings theoretical RNA hybridization model, the Examiner has cited the table of contents of Nicolau *et al.*, Handbook of Combinatorial Chemistry, Vol. 1, pages v-xxv. The Examiner has stated that applicants have not provided any scientific evidence that

"the compounds of Konings [RNA] would be expected to react any differently than the compounds of Kirkpatrick [small organic disulfides]."

The Examiner has also stated that "Konings et al. teach the therapeutic application of disulfides to the stomach and/or gastro intestinal tract" and "all three references [which would include Konings] teach the application of similar compounds (e.g. all three references teach asymmetric disulfides with heteroaromatic rings)." (Advisory Action, paragraph bridging pages 10-11.)

To these assertions, applicants urge reconsideration of the outstanding rejection in light of the following arguments and evidence.

A. RNA and Small Organic Disulfides do not Have the Same Chemical Reactivity

In stating that "the compounds of Konings would [not] be expected to react *any differently* than the compounds of Kirkpatrick," (emphasis added) the Examiner seems to be inferring that RNA and small organic disulfides have the same chemical reactivity. Applicants urge that one of skill in the art would not agree that RNA and small organic disulfides have the same chemical reactivity.

RNA is a biopolymer that reacts with other strands of RNA by hybridization, which is the result of the formation of hydrogen bonds between the bases of the RNA polymer. RNA molecules will not form covalent bonds with each other in a simple aqueous solution. Being a biopolymer, RNA will not inhibit enzymes by binding to an enzyme's active site.

The small molecule organic disulfide compounds of Kirkpatrick are not biopolymers. The compounds of Kirkpatrick do not hybridize to each other by hydrogen bonding. Instead, the disulfide bonds of the compounds of Kirkpatrick are capable of forming covalent bonds with each other by disulfide exchange. The compounds of Kirkpatrick are also capable of enzyme inhibition by forming covalent bonds with the thioredoxin enzyme.

B. The Konings Reference Itself Does Not Teach Its Method is Universal

The Examiner has disagreed that the teachings of Konings could be applied to "all compounds." (Advisory Action, pages 8, last paragraph.) Nowhere does Konings profess that the RNA pooling strategies discussed are applicable to "all compounds." Konings says "[w]e believe that this model is representative of many types of compounds." (Page 2718, first full paragraph.) Applicants contend that "many" does not mean "all." If Konings had believed that the pooling strategies discussed therein were universal, Konings would have used a

different word than "many." Konings states for the following reason why her model is not universally applicable to all combinatorial libraries.

> Cleary the merits of different deconvolution approaches depend on the relative activities of the compounds in the libraries. Thus validity of these predictions for libraries, such as those in Figure 1 depends on the similarity between activity distributions in our model systems and those in real libraries. (*Id.*)

Konings also states that "[i]terative deconvolution does not require fixed position pooling; any method for dividing the compounds into nonoverlapping subsets is allowed, *although it may not always be feasible*." (Page 2710, column 2, first partial paragraph.) Finally Konings cautions as follows.

> When mixtures of compounds are screened, however, the possibility exists that the most active compound will not be identified. The specific strategies employed for pooling and deconvolution will affect the likelihood of success. (Abstract)

In conclusion, Konings never asserts that her theoretical deconvolution techniques, based on the study of RNA hybridization are universally applicable or absolutely predictable.

C. The Konings Reference Discusses a Theoretical Model, Not a Well Known Technique

As discussed above, the Examiner has stated that the theoretical RNA hybridization model of Konings "could be used interchangeably" with the teachings of Kirkpatrick as "both methods were well known in the art at the time of filing." Applicants urge that a paper discussing a theoretical model for a technique should not be viewed as relating to a well known technique.

D. Konings Does Not Relate to Disulfides or Gastric Therapy

As mentioned previously, the Examiner has stated "Konings et al. teach the therapeutic application of disulfides to the stomach and/or gastro intestinal tract" and "all three references [which would include Konings] teach the application of similar compounds (e.g. all three references teach asymmetric disulfides with heteroaromatic rings)." (Advisory Action, paragraph bridging pages 10-11.)

Applicants maintain that this is an erroneous statement of fact. The Konings article relates to using RNA hybridization as a theoretical basis for studying deconvolution techniques. Nothing in Konings relates to disulfides or therapy of the stomach and/or gastro intestinal tract. A correction of the record is respectfully requested in the next communication from the Examiner.

E. Nicolaou Appears to Actually Teach Away from the Combination of Kirkpatrick and Konings

Applicants contend that Nicolaou does not support the proposition that RNA has the same chemical reactivity as small organic disulfides or that one of skill in the art would have found the teachings of Konings applicable to disulfides. It is true that the Nicolaou index covers a wide variety of topics related to combinatorial chemistry. A sampling of Nicolaou shows chapter topics such as instrumentation, addition to C-C multiple bonds, chemistry of the carbonyl group, solid-phase palladium catalysis for highthrough put organic synthesis, virtual compound libraries and molecular modeling, and combinatorial aspects of materials science.

What is noteworthy is that none of the listed chapters or subchapters of Nicolaou mention disulfides at all. Applicants contend that the omission of a discussion about disulfides is a teaching away from the present invention and is direct evidence that one of ordinary skill in the art would not have been motivated to arrive at the present invention.

F. The Attached Otto Reference Provides Further Scientific Evidence of the Differences of Disulfide Libraries

Applicants attach hereto Otto *et al.*, *J. Am. Chem. Soc.* 2000, 122, 12063-12064 (Otto), which evidences that there are unique considerations when working with disulfides. Otto defines dynamic combinatorial libraries (DCLs) as those that "differ from conventional combinatorial libraries in that the individual members of the library are constantly interconverting." (Page 1263, column 1, paragraph 2.) Otto states that "[a]t present, research on DCLs is still in the proof-of-principle stage." (Page 1263, column 1, paragraph 3.) Mechanistic studies on disulfides indicate, *inter alia*, that "disulfide exchange takes place efficiently under mild conditions in the presence of a catalytic amount of thiol." (Page 1263, column 2, paragraph 1.) Scheme 1 of Otto illustrates the swapping of small organic molecules by disulfide exchange. From a library of four different compounds, 119 different

macrocyclic compounds was confirmed. (Page 1264, column 1, paragraph 2.) As noted in footnote (18) at page 1264, there were problems with precipitation. In conclusion, applicants assert that Otto evidences that one of skill in the art would not have been motivated to combine Kirkpatrick and Konings because of problems associated with disulfide exchange.

II. Combination of Kirkpatrick and Fischli

The Examiner has cited the reference Fischli to support the position that it would have been ordinary obvious for one of skill in the art to choose for the R^8 position an alkyl with 1-10 carbon atoms substituted with an amine. The Examiner has stated that it would have been obvious to combine Kirkpatrick and Fischli for the following reasons.

(1) "[D]isulfides with benzimidazole and/or imidzole are preferred embodiment for high throughput screening against thioredoxin reductase/thioredoxin targets (e.g. Kirkpatrick et al., abstract see especially column 18, lines 24-25, which would encompass the compounds of Fischli et al. (Advisory Action, page 10, last paragraph.)

(2) "Fischli et al. teach that their disulfides are "gastric acid secretion-inhibiting and/or mucosa protecting" (e.g., see column 1, lines 66-67) which would be beneficial because Kirkpatrick et al. and Konings et al. [sic] teach the therapeutic application of disulfides to the stomach and/or gastrointestional tract would require such protection (see Kirkpatrick et al., "The term 'cancer' also refers to stomach cancer", see also column 3, lines 39; see column 8, line 58. (Id.)

(3) "[A]ll three references [sic] teach the application of similar compounds (e.g. all three references [sic] teach asymmetric disulfides with heteroaromatic rings." (Advisory Action, page 11, top partial paragraph.)

To these arguments of the Examiner, applicants respond as follows.

A. There is No Nexus Between Kirkpatrick and Fischli

Kirkpatrick teaches the use of disulfides to inhibit thioredoxin/thioreductase enzymes to treat cancer. Kirkpatrick provides in vivo results in a mouse model against one type of cancer: breast cancer. (See page Table 2). Kirkpatrick does speculate on usefulness against other stomach or gastrointestinal cancer as follows:

"The asymmetrical disulfides of the present invention are particularly useful to treat cancers, more particularly, cancers such as myeloma, cervical, lung, gastric, colon, renal, prostate, and breast cancers." (Column 3, lines 35-40).

"Thioredoxin protein levels are elevated in a variety of human primary tumors including human cervical neoplastic squamous epithelial cells, gastric carcinoma, and hepatocellular carcinoma." (Column, lines 56-59).

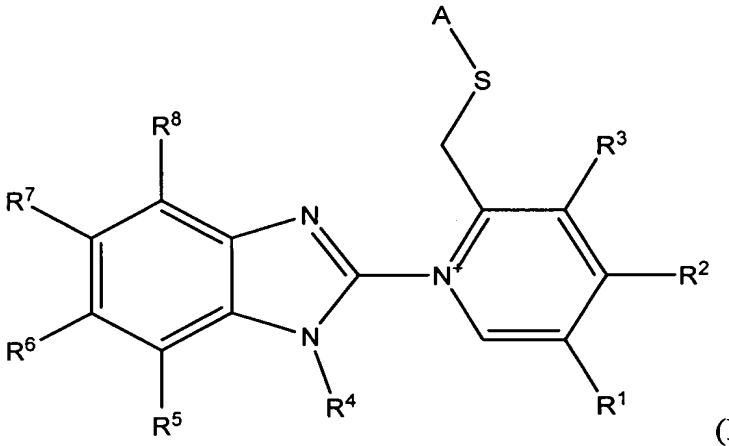
Kirkpatrick has no disclosure related to gastric acid secretion inhibition or muscosa protection.

Fischli teaches that his compounds have "gastric acid secretion-inhibiting properties and/or muscosa protecting properties (especially against indomethhacin-induced lesions)." Fischli does not disclose a mechanism of action. Fischli does not discuss cancer treatment.

Applicants contend that the Examiner has not established why one of skill in the art would think that any substituent of a compound with potential to treat excess gastric acid would also be an interchangeable with any substituent of a compound that is speculated as being useful to treat cancer.

B. The Examiner Is Not Viewing the Fischli References as a Whole

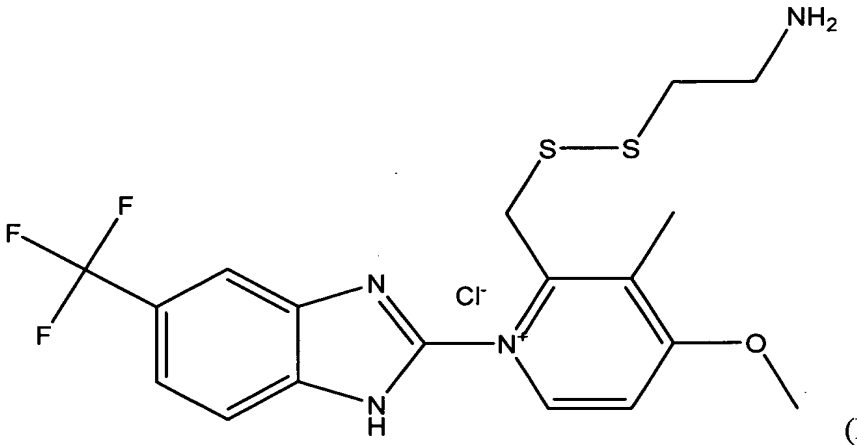
Fischli discloses a total of 17 compounds. (See Table of column 12). Of these compounds, only one compound, compound G, happens to have a 2-aminoethyl. As a whole Fischli relates to compounds of the following genus of Formula (I):



(I)

wherein A is $-SR^3$, $-SO_3^-$ or $-S-SO_3^-$.

Compound G of Fischli has the following structure



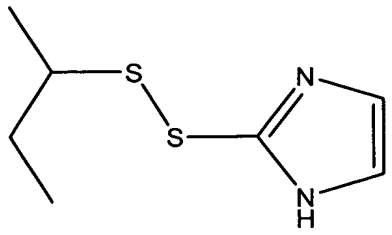
(II)

Fischli does not discuss any particular advantage of the properties of a the 2-aminoethyl or any rational for using the 2-aminoethyl. Of 17 compounds actually made, only one had a 2-aminoethyl substituent. Statistically speaking, 1/17 is a 5.9% chance.

By randomly picking out the species of all of the possible members of the Markush group of Fischli, the Examiner is not viewing the teaching of Fischli as a whole and is engaging in hindsight. The Examiner has simply not demonstrated why, without any impressible hindsight guidance, one of ordinary skill in the art would (1) combine references related to cancer and gastric acid (2) out of 17 compounds in the gastric acid reference identify and pick out compound G as desirable, then (3) pick out one substituent of compound G out of 4 substituents, then (4) combine this one part of compound G (2-aminoethyl) with the compounds for treating cancer and finally (5) make an entire combinatorial library base on this one part of one compound.

C. Kirkpatrick and Fischli Do Not Teach Analogous Disulfides

The lead compound of Kirkpatrick has the following structure:



(III)

(See column 17, lines 11-14, which describe this compound as the lead compound.)

Kirkpatrick teaches 27 possible ring structures in Figure 9 that may be used in one of the R positions of an asymmetrical disulfide R^1-S-S-R^2 wherein one of R^1 or R^2 would be represented by R. Of these 27 possible compounds three are types of imidazyols and one is a carboxylic acid pyrimidinyl. In contrast, Fischli teaches the equivalent of an R^1-R^2-S-S-R^3, wherein R^1 is a trifluoromethyl substituted imidazoyl, R^2 is a trisubstituted pyrimidinyl and R^3 is a 2-aminoethyl. There is simply no suggestion in Kirkpatrick of such an R^1-R^2-S-S-R^3 moiety

D. There Would be No Motivation to Choose Compound G of Fischli

As applicants have previously stated, Fischli made 17 compounds. The anti-ulcer ED_{50} mg/kg p.o. of these compounds ranged from 1.2 to 2.5 (G was 2.3) and the gastric acid secretion inhibition, ED_{50} mg/kg p.o. ranged from 1.5 to 6.8 (G was 6.2). Compound G, however, was among the compounds with the worst toxicity profile. Specifically, the desirable LD_{50}mg/kg p.o. of Compound G was between 312-625, whereas other compounds had a value of over 5000.

Applicants therefore urge that in light of these facts, one of skill in the art would have to (1) combine references related cancer and gastric acid (2) out of 17 compounds in the gastric acid reference identify and pick out compound G as desirable, then (3) pick out one substituent of compound G out of 4 substituents, then (4) combine this one part of compound G (2-aminoethyl) with the compounds for treating cancer and finally (5) make an entire combinatorial library base on this one part of one compound useful in treating cancer.

Without impressible hindsight based on the teachings of the present specification one of ordinary skill in the art would not have been motivated to combine Kirkpatrick and Fischli. Accordingly, applicants urge that the present claims to be in condition for allowance. The Examiner is invited to contact the undersigned by telephone to advance prosecution of this application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or

even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Respectfully submitted,

February 9, 2005
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